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PATENT SPECIFICATION

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1401518

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(54) ANTI-ACNE COMPOSITIONS

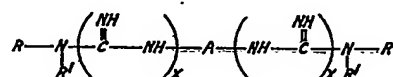
(71) We, MERCK & CO. INC., a corporation duly organised and existing under the laws of the State of New Jersey, United States of America, of Rahway, New Jersey, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to anti-acne agents.

Although the precise etiology of acne vulgaris has not been completely traced, the pattern of the disease is well known. Lipases of bacterial origin give rise to the fatty acids which somehow cause the characteristic comedones. Certain bacteria invariably accompany this disease and often cause unsightly blemishes which sometimes leave permanent scars.

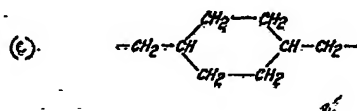
Topical anti-acne agents has long been used in treatment of acne, but until now with less than satisfactory results. Phenolics (such as phenol, hexachlorophene, dichlorometaxlenols, *p*-chlorometaxlenol) are inactivated by organic load, and in many instances, by soap. For these and for other reasons, they fail in acne. Quaternary ammonium surfactants are inactivated by protein load, by soap and by hard water. They, too, have not displayed great efficacy in acne.

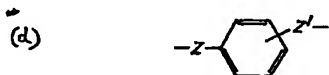
In accordance with the present invention, there is provided a topically administrable anti-acne pharmaceutical preparation in the form of a jelly, an emulsion or an unflavoured lotion comprising an inert pharmaceutical carrier and at least one compound of the formula:



or a pharmaceutically acceptable salt thereof, in which R is C₆₋₁₈ alkyl, alkoxyalkyl or alkylthioalkyl, R' is hydrogen or lower alkyl, x is 1 or 2 and A is

- (a) C₂₋₁₂ alkylene having the valency bonds attached to different carbon atoms,
 (b) —(CH₂)_m—Y—(CH₂)_n— where each of m and n is an integer ranging from 2 to 6 and Y is O or S,

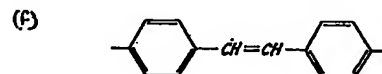




where each of Z and Z' is C₁₋₃ alkylene,



in which Q is -O-, -S-, -SO- or -SO₂-, or



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It has been found that agents used in the compositions of the present invention have broad anti-acne spectra, are highly potent against *Corynebacterium acnes* and *Staphylococcus epidermis*, the microbes most commonly found in acne postules. Such compounds are highly substantive to skin, penetrate into the skin, tolerate reasonable amounts of soap and organic matter, and are bactericidal at low concentrations.

Continuous research has shown that at least compounds mentioned below have not led to emergence of resistant strains, and have activity against strains that have developed resistance to tetracycline, a common acne treatment. Also, continuous research has shown that the class of anti-acne agents included herein are potent lipase inhibitors.

The preferred bis-biguanide compounds disclosed herein possessing novel anti-acne activity are:

- 1,1'-hexamethylenebis[5-(n-heptyl)-biguanide]
- 1,1'-hexamethylenebis[5-(n-octyl)-biguanide]
- 1,1'-hexamethylenebis[5-(2-ethylhexyl)-biguanide]
- 1,1'-hexamethylenebis[5-nonylbiguanide]
- 1,1'-hexamethylenebis[3-hexylbiguanide]
- 1,1'-hexamethylenebis[3-octylbiguanide]
- 1,1'-hexamethylenebis[5-(3-ethoxyethyl)-biguanide]
- 1,1'-hexamethylenebis[5-(3-isobutoxypropyl)-biguanide]
- 1,1'-(2-chloro-p-xylylene)bis[5-octylbiguanide]

Other representative compounds within the scope of the invention are:

- 1,1'-hexamethylenebis[5-hexylbiguanide]
- 1,1'-hexamethylenebis[5-(1,1,3,3-tetramethylbutyl)-biguanide]
- 1,1'-hexamethylenebis[5-(2-ethylhexyl)-biguanide]-cobalt complex
- 1,1'-hexamethylenebis[5-dodecylbiguanide]
- 1,1'-hexamethylenebis[5-decylbiguanide]
- 1,1'-hexamethylenebis[3-decylbiguanide]
- 1,1'-hexamethylenebis[5-(3-isopropylmercaptopropyl)-biguanide]
- 1,1'-hexamethylenebis[5-(6-methylmercaptohexyl)-biguanide]
- 1,1'-hexamethylenebis[5-(7-methylmercaptoheptyl)-biguanide]
- 1,1'-hexamethylenebis[5-(4-pentylmercaptobutyl)-biguanide]
- 1,1'-hexamethylenebis[5-(8-methylmercaptooctyl)-biguanide]
- 1,1'-hexamethylenebis[5-(2-hexyloxy-1-methylethyl)-biguanide]
- 1,1'-hexamethylenebis[5-(2-propyloxy-1-methylethyl)-biguanide]
- 1,1'-hexamethylenebis[5-(4-propyloxy-1-methylbutyl)-biguanide]
- 1,1'-hexamethylenebis[5-(7-methoxyheptyl)-biguanide]
- 1,1'-hexamethylenebis[5-(3-isopropoxypropyl)-biguanide]
- 1,1'-hexamethylenebis[5-(3-propoxypropyl)-biguanide]
- 1,1'-hexamethylenebis[5-hexadecylbiguanide]
- 1,1'-hexamethylenebis[5-tetradecylbiguanide]
- 1,1'-hexamethylenebis[5-(4,8,12-trimethyltridecyl)-biguanide]
- 1,1'-(2-methyl-1,4-butylene)bis[5-heptylbiguanide]
- 1,1'-(p-xylylene)bis[5-(2-ethylhexyl)-biguanide]
- 1,1'-(2,3,5,6-tetrachloro-p-xylylene)bis[5-(2-ethylhexyl)-biguanide]
- 1,1'-octamethylenebis[5-hexyl-5-methylbiguanide]
- 1,1'-(2,3,5,6-tetramethyl-p-xylylene)bis[5-(2-ethylhexyl)-biguanide]

- 1,1'-[*p*-phenylenebis(ethylene)]bis[5-octylbiguanide]
 1,1'-[oxybis(*p*-phenylene)]bis[5-octylbiguanide]
 1,1'-oxybis[propylene]bis[5-ethyl-5-(1,3-dimethyl-3-methylmercaptobutyl)-
 biguanide]
 5 1,1'-oxybis[propylene]bis[5-methyl-5-(1-ethyl-2-methylmercaptopropyl)-
 biguanide] 5
 1,1'-oxybis[propylene]bis[5-ethyl-5-hexylbiguanide]
 1,1'-(2,5-dimethyl)-*p*-phenylenebis(ethylene)bis[5-hexylbiguanide]
 1,1'-[phenylenebis(1-methylethylene)]bis[5-hexylbiguanide]
 10 1,1'-[1,4-cyclohexanebis(methylene)]bis[5-hexylbiguanide] 10
 1,1'-thiobis[*p*-phenylene]bis[5-octylbiguanide]
 1,1'-sulfinylbis[*p*-phenylene]bis[5-octylbiguanide]
 1,1'-sulfonylbis[*p*-phenylene]bis[5-octylbiguanide]
 15 1,1'-(4,4'-stilbene)bis[5-octylbiguanide] 15
 1,1'-(1,3-xylylene)bis[5-octylbiguanide]
 1,1'-(1,2-xylylene)bis[5-octylbiguanide]
 1,1'-thiobis[ethylene]bis[5-octylbiguanide]
 1,1'-thiobis[propylene]bis[5-octylbiguanide]
 1,1'-oxybis[butylene]bis[5-octylbiguanide]

20 The compounds of this invention are administered in topical form at doses
 ranging from about 0.01% to 0.5% by weight of the composition. Of particular
 preference is from about 0.02% to 0.1% by weight of the active ingredient to the
 total weight of the composition. The formulations included herein are effective
 in the treatment of acne conditions in humans.

25 It will be understood, however, that the specific dose level for any particular
 patient will depend upon a variety of factors including the activity of the specific
 compound employed, the age, body weight, general health, sex, diet, time of ad-
 ministration, rate of excretion, drug combination and the severity of the acne on the
 particular area undergoing therapy.

30 The pharmaceutical compositions may be prepared according to any method
 known for the manufacture of such compositions and where appropriate may contain
 as much as 99.99% of the total formulation weight of one or more miscible non-toxic
 surfactants, solvents and/or emollient agents, e.g. alkanols such as methanol, ethanol
 and isopropanol; 2-octyl dodecanol, methyl pyrrolidone, squalene, squalane, isopar
 35 "M" (coparaflinate), isopropyl myristate, acetulan (acetylated lanolin alcohols), poly-
 ethylene glycol, diethylphthalate, polysorbate 80, Ceraphyl 230 (diisopropyl adipate),
 mineral oil, propylene glycol, water, glycerine, salicylic acid, perfume, coloring
 agents, aqueous citrate-phosphate buffer, benzyl alcohol, dipropylene glycol and
 nonoxynol.

40 The use of pharmaceutically acceptable salts of the compounds included herein
 is to be considered within the scope of the invention. Representative examples of
 said pharmaceutically acceptable salts are the mono- or di-hydrohalide, sulfamate,
 saccharin, tartrate, acetate, sulfate, phthalate, succinate, citrate, lactate and nitrate.

45 The compounds employed in this invention are known from U.S. Patent
 3,468,898, wherein they are taught as antibacterial agents, and U.K. Patent No.
 1,095,902. Attention is directed to the latter patent in view of Section 9 of the
 Patents Act, 1949.

The following examples illustrate the preparation of the various acne inhibitor
 compositions of the invention.

50	Example 1			50
	Acne Lotion		% By Weight	
	Ethyl alcohol		45	
	Salicylic acid		0.5	
55	1,1'-hexamethylenebis[5-(2-ethylhexyl)-biguanide] . 2HCl		0.1	
	Water		54.4	55
	Perfume and color, q.s.			

To the ethyl alcohol is added 1,1'- hexamethylene - bis[5 - (2 - ethylhexyl) -
 biguanide] . 2HCl, salicylic acid, water, and, optionally, perfume and coloring.

60 When other potent anti-acne agents such as 1,1'- hexamethylenebis[5 - (*n* -
 heptyl) - biguanide]; 1,1'- hexamethylene - bis[5 - (*n* - octyl) - biguanide]; 1,1'-
 hexamethylenebis[5 - nonyl - biguanide]; 1,1'- hexamethylenebis[3 - hexylbiguanide];
 1,1'- hexamethylenebis[3 - octylbiguanide]; 1,1'- hexamethylenebis - [5 - (2 -

ethoxyethyl) - biguanide]; 1,1' - hexamethylenebis[5 - (3 - isobutoxypropyl) - biguanide]; or 1,1' - (2 - chloro - p - xylylene) - bis[5 - octylbiguanide] is substituted for 1,1' - hexamethylenebis[5 - (2 - ethylhexyl) - biguanide], there is obtained the corresponding product.

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Example 2

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Acne Facial Freshener Lotion

% By Weight

Isopropyl alcohol	29.9
1,1'-hexamethylenebis[5-(2-ethylhexyl)-biguanide] .2HCl	0.1
Aqueous citrate-phosphate buffer to pH=5.5	70.0
Perfume and color, q.s.	

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To an aqueous citrate-phosphate buffer solution at pH 5.5 is added, with agitation, a mixture of 1,1' - hexamethylenebis[5 - (2 - ethylhexyl) - biguanide] .2HCl and isopropyl alcohol. Fragrance and color may be added to suit.

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When other anti-acne agents such as 1,1' - hexamethylenebis[5 - (n - heptyl) - biguanide]; 1,1' - hexamethylenebis[5 - (n - octyl) - biguanide]; 1,1' - hexamethylenebis[5 - nonylbiguanide]; 1,1' - hexamethylenebis[3 - hexylguanide]; 1,1' - hexamethylenebis[3 - octylguanide]; 1,1' - hexamethylenebis[5 - (2 - ethoxyethyl) - biguanide]; 1,1' - hexamethylenebis[5 - (3 - isobutoxypropyl) - biguanide]; or 1,1' - (2 - chloro - p - xylylene) - bis[5 - octylbiguanide] is substituted for 1,1' - hexamethylenebis[5 - (2 - ethylhexyl) - biguanide], there is obtained the corresponding product.

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Example 3

Moisturizing Lotion

% By Weight

Isopropyl alcohol	25.00
Propylene glycol	10.00
1,1'-hexamethylenebis[5-(2-ethylhexyl)-biguanide] .2HCl	0.05
Water	64.95
Perfume and color, q.s.	

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To an isopropyl alcohol-propylene glycol solution is added, with agitation, 1,1' - hexamethylenebis[5 - (2 - ethylhexyl) - biguanide] .2HCl, water, perfume and coloring.

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When other anti-acne agents such as 1,1' - hexamethylenebis[5 - (n - heptyl) - biguanide]; 1,1' - hexamethylenebis[5 - (n - octyl) - biguanide]; 1,1' - hexamethylenebis[5 - nonylbiguanide]; 1,1' - hexamethylenebis[3 - hexylguanide]; 1,1' - hexamethylenebis[3 - octylguanide]; 1,1' - hexamethylenebis[5 - (2 - ethoxyethyl) - biguanide]; 1,1' - hexamethylenebis[5 - (3 - isobutoxypropyl) - biguanide]; or 1,1' - (2 - chloro - p - xylylene) - bis[5 - octylbiguanide] is substituted for 1,1' - hexamethylenebis[5 - (2 - ethylhexyl) - biguanide], there is obtained the corresponding product.

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Example 4

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Moisturizing Lotion

% By Weight

Isopropyl alcohol	25.00
Glycerine	10.00
1,1'-hexamethylenebis[5-(2-ethylhexyl)-biguanide] .2HCl	0.05
Water	64.95
Perfume and color, q.s.	

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To isopropyl alcohol is added, with agitation, 1,1' - hexamethylenebis[5 - (2 - ethylhexyl) - biguanide] .2HCl, glycerine, water, perfume and coloring.

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When other anti-acne agents such as 1,1' - hexamethylenebis[5 - (n - heptyl) - biguanide]; 1,1' - hexamethylenebis[5 - (n - octyl) - biguanide]; 1,1' - hexamethylenebis[5 - (nonylbiguanide)]; 1,1' - hexamethylenebis[3 - hexylguanide]; 1,1' - hexamethylenebis[3 - octylguanide]; 1,1' - hexamethylenebis[5 - (2 - ethoxyethyl) - biguanide]; 1,1' - hexamethylenebis[5 - (3 - isobutoxypropyl) - biguanide]; or 1,1' - (2 - chloro - p - xylylene) - bis[5 - octylbiguanide] is substituted for 1,1' - hexamethylenebis[5 - (2 - ethylhexyl) - biguanide], there is obtained the corresponding product.

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Example 5

Acne Lotion, Emulsion		% By Weight	
5	1,1'-hexamethylenebis[5-(2-ethylhexyl)-biguanide].2HCl	0.1	
	Propylene glycol	2.5	
	Ethoxylated lanoline alcohols	3.2	5
	Mineral oil	3.8	
	Cetyl alcohol	1.1	
10	Glycerol monostearate	4.0	
	Water, q.s. ad.	100.0	
	Perfume and color, q.s.		10

To a mixture which contains mineral oil, cetyl alcohol, glycerol monostearate and ethoxylated lanolin alcohols at 80°C. is added a solution containing 1,1' - hexamethylenebis[5 - (2 - ethylhexyl) - biguanide] .2HCl, propylene glycol and water. The resulting mixture is then cooled to room temperature with agitation.

- 15 When other anti-acne such as 1,1' - hexamethylenebis[5 - (n - heptyl) - biguanide]; 1,1' - hexamethylenebis[5 - (n - octyl) - biguanide]; 1,1' - hexamethylenebis[5 - nonylbiguanide]; 1,1' - hexamethylenebis[3 - hexylguanide]; 1,1' - hexamethylenebis[3 - octylguanide]; 1,1' - hexamethylenebis[5 - (2 - ethoxyethyl) - biguanide]; 1,1' - hexamethylenebis[5 - (3 - isobutoxypropyl) - biguanide]; or 1,1' - (2 - chloro - p - xylylene) - bis[5 - octylbiguanide] is substituted for 1,1' - hexamethylenebis[5 - (2 - ethylhexyl) - biguanide], there is obtained the corresponding product.
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Example 6

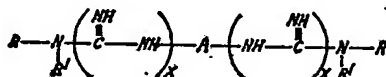
Acne Lotion		% By Weight	
25	Isopropyl alcohol	45.0	25
	1,1'-hexamethylenebis[5-(2-ethylhexyl)-biguanide].2HCl	0.1	
	Aqueous citrate-phosphate buffer to pH=5.5		
	Perfume and color, q.s.		

To an aqueous citrate-phosphate buffer solution at pH 5.5 is added, with agitation, a mixture which contains 1,1' - hexamethylenebis[5 - (2 - ethylhexyl) - biguanide] .2HCl and isopropyl alcohol. Fragrance and color may be added to suit.

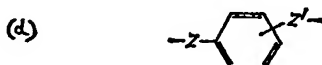
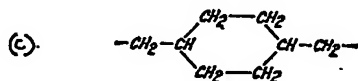
- 30 When other anti-acne agents such as 1,1' - hexamethylenebis[5 - (n - heptyl) - biguanide]; 1,1' - hexamethylenebis[5 - (n - octyl) - biguanide]; 1,1' - hexamethylenebis[5 - nonylbiguanide]; 1,1' - hexamethylenebis[3 - hexylguanide]; 1,1' - hexamethylenebis[3 - octylguanide]; 1,1' - hexamethylenebis[5 - (2 - ethoxyethyl) - biguanide]; 1,1' - hexamethylenebis[5 - (3 - isobutoxypropyl) - biguanide]; or 1,1' - (2 - chloro - p - xylylene) - bis[5 - octylbiguanide] is substituted for 1,1' - hexamethylenebis[5 - (2 - ethylhexyl) - biguanide], there is obtained the corresponding product.
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WHAT WE CLAIM IS:—

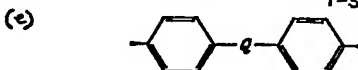
- 40 1. A topically administrable anti-acne pharmaceutical composition in the form of a jelly comprising an inert pharmaceutical carrier and at least one compound of the formula:



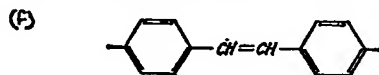
- 45 or a pharmaceutically acceptable salt thereof, in which R is C₆₋₁₀ alkyl, alkoxyalkyl or alkylthioalkyl, R' is hydrogen or lower alkyl, α is 1 or 2 and A is
- (a) C₂₋₁₂ alkylene having the valency bonds attached to different carbon atoms,
- (b) $-(CH_2)_m-Y-(CH_2)_n-$ where each of m and n is an integer ranging from 2 to 6 and Y is O or S,
- 50



where each of Z and Z' is C₁₋₃ alkylene,



in which Q is -O-, -S-, -SO- or -SO₂-, or



2. A topically administrable anti-acne pharmaceutical composition in the form of an emulsion comprising an inert pharmaceutical carrier and at least one compound of the formula set forth in Claim 1.

3. A topically administrable anti-acne pharmaceutical composition in the form of an unflavoured lotion comprising an inert pharmaceutical carrier and at least one compound of the formula set forth in Claim 1.

4. A preparation as claimed in Claim 3, containing isopropanol.

5. A composition according to any preceding claim in which A is alkylene, R is alkyl, and R' is hydrogen.

6. A composition according to Claim 3 in which the compound is 1,1'-hexamethylenebis[5-(n-heptyl)-biguanide].

7. A composition according to Claim 3 in which the compound is 1,1'-hexamethylenebis[5-(n-octyl)-bi-guanide].

8. A composition according to Claim 3 in which the compound is 1,1'-hexamethylenebis[5-(2-ethylhexyl)-biguanide].

9. A composition according to Claim 3 in which the compound is

1,1'-hexamethylenebis[5-(nonyl)-biguanide];
1,1'-hexamethylenebis[3-(hexyl)-guanide];
1,1'-hexamethylenebis[3-(octyl)-guanide];
1,1'-hexamethylenebis[5-(hexyl)-biguanide];
1,1'-hexamethylenebis[5-(1,1,3,3-tetramethylbutyl)-biguanide];
1,1'-(2-methyl-1,4-butylene)bis[5-(heptyl)-biguanide]; or
1,1'-hexamethylenebis[5-(decyl)-biguanide].

10. A composition as claimed in any one of Claims 1—9 containing 0.01 to 0.5% by weight of the said compound.

11. A composition as claimed in Claim 10 containing 0.02 to 0.1% by weight of the said compound.

12. A composition according to any one of Claims 1—11 containing, in addition to the carrier and the said compound, at least one of the following ingredients, viz. salicylic acid, a perfume, a colouring agent, a buffering agent, glycerine, a surface-active agent or an emulsifying agent.

13. A composition according to Claim 4, substantially as hereinbefore described in any one of the Examples.

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